enablement rejection, discussed below. In addition, Applicants have amended the specification to attach the revised Sequence Listing. Thus, Applicants have not introduced new matter by these amendments and claims 60 and 80 remain pending and at issue.

**Amendment to the Sequence Listing Under 37 C.F.R. § 1.825**

The Examiner asserted that the December 11, 2001 communication (received January 31, 2002) is not fully responsive to the previous official action for the reason(s) set forth on the March 8, 2002 Notice to Comply with the Sequence Rules. Accordingly, Applicants have amended the Sequence Listing as suggested in the March 8, 2002 Notice to Comply. Submitted herewith is a paper copy of the Sequence Listing under 37 C.F.R. § 1.821(c), together with a substitute copy of the computer readable form under 37 C.F.R. § 1.821(e). Applicants aver that the paper copy of the Sequence Listing is identical to that contained on the computer readable form and that the substitute Sequence Listing does not include new matter.

**Rejection Under 35 U.S.C. § 112, First Paragraph**

Claims 60-61 and 80-81 were rejected under 35 U.S.C. § 112, first paragraph, as non-enabling. In particular, the Examiner noted that while the specification is enabling for certain compounds that exhibit 100-fold or 500-fold selectivity for TACE over MMP-1, he contends that the specification does not reasonably enable any compound that exhibits such selectivity. The Examiner offered the following comments in support of the rejection:

> The claims as amended now recite a specific degree of selectivity, 100-fold or 500-fold for TACE over MMP1. The specification at Table A provides evidence for specific compounds which can meet these claims. However, more compounds fail to meet these limitations than meet them. This suggests that there is a high degree of unpredictability in the selection of suitable inhibitors. The lack of measurement of inhibition of both enzymes in prior art references was discussed in the Office action of 11 July 2001. This renders it difficult to predict from the observation of TACE inhibition that a given inhibitor will exhibit the required selectivity. There are no clear structural elements or requirements that have been described in the instant disclosure that would lead a person of ordinary skill in the art to select a particular inhibitor. Office Action at 3.
>
> The instant specification provides absolutely no guidance as to which structural elements or features are essential for the functional selectivity as claimed. Further, there is no functionally and structurally analogous inhibitors which have been identified in the prior art for which this information is known and could be extrapolated to the instant inhibitors by analogy. In conclusion, the instant claims encompass a vast, almost limitless, number of inhibitors and yet the instant specification provides limited specific working examples and no general guidance that would permit and [sp] artisan to practice the invention commensurate with the scope of the instant claims. Office Action at 5.

Without conceding the propriety of the rejection and purely in the interests of advancing the prosecution of the instant application, Applicants have canceled claims 60 and 80. Applicants reserve the right to pursue claims 60 and 80 in a subsequent divisional application. However, claims 61 and 81 remain pending and they are reproduced below for ease of reference:

> 61. A method of inhibiting the cleavage of TNF-β from cell membranes without inhibiting MMP-1 in a mammal comprising administering to such mammal an effective amount of a hydroxamic acid compound that possesses at least 100 fold $IC_{50}$ selectivity for TACE over MMP-1; wherein MMP-1 activity is determined by an MMP-1 in vitro assay and wherein TACE activity is determined by a human monocyte assay.
>
> 81. A method of inhibiting the cleavage of TNF-β from cell membranes without inhibiting MMP-1 in a mammal comprising administering to such mammal an effective amount of a hydroxamic acid compound that possesses at least 500 fold $IC_{50}$ selectivity for TACE over MMP-1; wherein MMP-1 activity is determined by an MMP-1 in vitro assay and wherein TACE activity is determined by a human monocyte assay.

Therefore, the instant claims are specifically directed to a method of inhibiting the cleavage of TNF-α without inhibiting MMP-1 by administering a hydroxamic acid compound that is selective for TACE over MMP-1. Applicants note that claims 61 and 81 were pending at the time the April 16, 2002 Official Action was issued, but based on the Examiner's comments, he appears to have focused on claims 60 and 80 in formulating his arguments. In particular, the Examiner asserted that the instant claims did not include clear structural elements that would guide the skilled artisan to identify compounds having the claimed functional selectivity (see, e.g., pages 3 and 5 of the Office Action, excerpted above). However, claims 61 and 81 specifically call for the administration of a hydroxamic acid compound, which is a distinct structural element that clearly identifies the class of compounds that is the basis for the present invention.

The claims call for a method of inhibiting the cleavage of TNF-β from cell membranes without inhibiting MMP-1 in a mammal by administering an effective amount of a hydroxamic acid compound that possesses at least 100-500 fold $IC_{50}$ selectivity for TACE over MMP-1, wherein MMP-1 activity is determined by an MMP-1 in vitro assay and TACE activity is determined by a human monocyte assay. Thus, in order to enable the full scope of these claims, the subject specification, coupled with what is known in the art, must provide the skilled artisan the ability to do the following:

(a) assay the inhibition of TNF-β cleavage from cell membranes using a human monocyte assay;

(b) assay the inhibition of MMP-1 activity using an MMP-1 in vitro assay; and

(c) identify a hydroxamic acid compound that possesses at least 100-500 fold $IC_{50}$ selectivity for TACE over MMP-1 based on assays (a) and (b).

A careful review of the subject specification clearly shows that each of these elements are described in the specification. First, at page 44 the specification provides the protocol for a human monocyte assay with which one can readily assess the relative inhibition of TNF-β cleavage from cell membranes. Thus, element (a) is provided by the subject specification. Element (b) is also provided; at page 45 the specification provides the protocol for an assay to determine the inhibition of human collagenase (MMP-1). Finally, the specification provides hydroxamic acid compounds that possess the requisite selectivity for TACE over MMP-1 based on assays (a) and (b). In particular, the Examiner's attention is directed to Table A, pages 42-44 of the subject specification, which provides a number of hydroxamic acid compounds that were tested by these methods. Of the 8 hydroxamic acid compounds tested, 6 were found to have at least 100 fold $IC_{50}$ selectivity for TACE over MMP-1.

The Examiner previously commented that "[t]he instant disclosure does not provide any teachings which would lead an ordinary artisan to believe that a general structure whose compounds mostly exhibit such selectivity has been disclosed" (July 11, 2001 Official Action at 5). This is simply not true. As Table A shows, a variety of hydroxamic acid compounds have been disclosed and tested for TACE/MMP-1 selectivity, and a majority of those disclosed possess the claimed selectivity. Moreover, the specification provides even more hydroxamic acid compounds in the Examples that may be tested using the assays mentioned above to identify even more compounds having the requisite selectivity. Finally, the present claims call for a hydroxamic acid compound having at least 100 fold selectivity for TACE once MMP 1, which are obtainable from Applicants' teachings plus ordinary skill. In this regard, Applicants once again call the following U.S. Patents to the Examiner's attention, which are directed to small molecules, e.g. hydroxamic acid compounds that inhibit TACE and using the assays disclosed in the specification, one can readily identify compounds that exhibit the required selectivity:

- U.S. Patent No. 6,326,516, entitled "Acetylenic □-sulfonamido and phosphinic acid amide hydroxamic acid TACE inhibitors";
- U.S. Patent No. 6,313,123, entitled "Acetylenic sulfonamide thiol TACE inhibitors;
- U.S. Patent No. 6,277,885, entitled "Acetylenic aryl sulfonamide and phosphinic acid amide hydroxamic acid TACE inhibitors;
- U.S. Patent No. 6,225,314, entitled "Inhibition of matrix metalloproteases by substituted biaryl oxobutyric acids;
- U.S. Patent No. 6,225,311, entitled "Acetylenic □-amino acid-based sulfonamide hydroxamic acid TACE inhibitors;
- U.S. Patent No. 6,200,996, entitled "Heteroaryl acetylenic sulfonamide and phosphinic acid amide hydroxamic acid TACE inhibitors;
- U.S. Patent No. 6,197,795, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;
- U.S. Patent No. 6,162,821, entitled "Preparation and use of ortho-sulfonamide heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;

- U.S. Patent No. 6,162,814, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metaloproteinase and TACE inhibitors;
- U.S. Patent No. 5,977,408, entitled "Preparation and use of □-sulfonamido hydroxamic acids as matrix metalloproteinase and TACE inhibitors;
- U.S. Patent No. 5,968,795, entitled "Biaryl acetylenes as inhibitors of matrix metalloproteases;
- U.S. Patent No. 5,962,481, entitled "Preparation and use of ortho-sulfonamido heteroaryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;
- U.S. Patent No. 5,932,763, entitled "Inhibition of matrix metalloproteases by 2-(.omega.-arolalkyl)-4-biaryl-4-oxobutyric acids;
- U.S. Patent No. 5,929,097, entitled "Preparation and use of ortho-sulfonamido aryl hydroxamic acids as matrix metalloproteinase and TACE inhibitors;
- U.S. Patent No. 5,925,637, entitled "Inhibition of matrix metalloproteases by substituted biaryl oxobutyric acids;
- U.S. Patent No. 5,804,581, entitled "Inhibition of matrix metalloproteases by substituted phenalkyl compounds; and
- U.S. Patent No. 5,677,282, entitled "Amino acid amides of 1,3,4-thiadiazoles as matrix metalloproteinase.

The test of enablement is whether one skilled in the art could make or use the invention relying on the disclosure in the patent coupled with information known in the art without undue experimentation. *U.S. v. Telectronics, Inc.* 8 USPQ2d 1217, 1223 (Fed. Cir. 1988); M.P.E.P. § 2164.01. The factors used to elucidate whether undue experimentation is needed to practice the invention may include: (1) the nature of the invention, (2) the state of the prior art, (3) the level of predictability in the art, (4) the amount of direction or guidance present, (5) the existence of working examples, (6) the breadth of the claims, (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure, and (8) the level of one of ordinary skill in the art. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

> Moreover, by law a patent application is presumptively enabled when filed, i.e.,
>
> a specification . . . must be taken as in compliance with the enablement requirement . . . unless there is reason to doubt the objective truth of the statements contained therein which must relied on for enabling support." *In re Marzocchi*, 439 F.2d, 220, 223 (CCPA 1971).

As stated in the *Section 112 Enablement Training Manual*, the case law clearly provides that properly reasoned and supported statements explaining any failure to comply with Section 112 are required to support a rejection. If the examiner establishes a *prima facie* case of nonenablement through adequate evidence and reasoning, the burden shifts to the applicants to rebut the examiner's contentions.

Applicants have submitted an enabling disclosure including the use of exemplified compounds that are believed to be the best mode, see Table A, pages 42-44 of the specification as originally filed. Applicants have also described multiple synthetic schemes that could be used by one skilled in the art to prepare the claimed compounds and Applicants have also described several TACE and MMP-1 assays that demonstrate the utility of the claimed

compounds. Applicants have also provided a detailed description of methods for dosing and formulating the compounds of the invention. The Examiner has not challenged Applicants' disclosure on any of these points.

Instead, the Examiner's analysis is conclusory; simple declarative statements that one skilled in the art would not know how to make or use the claimed invention are inadequate – the Examiner must state *why* one would question the enablement of the claims. The Examiner has concluded that the specification does not reasonably enable other compounds having the desired selectivity, seemingly based on the number of compounds that have been shown in the specification in view of the possible number of compounds that could arguably be encompassed by the claims. However, he fails to state *why* the skilled artisan would not be assured that the claimed method could be reduced to practice by the skilled artisan based on the instant disclosure and the advanced state of the art. Applicants reiterate, the claims are limited to hydroxamic acid compounds, and Applicants have provided quite a number of such compounds that meet the limitations of the claims. Applicants have also provided the means for identifying other hydroxamic acid compounds that meet the claim limitations, and a plethora of hydroxamic acid compounds are known in the art.

Moreover, *In re Wands* provides the standard for determining whether an application complies with Section 112, first paragraph. Applicants submit the following analysis of the *Wands* factors to more clearly show that the subject specification is enabling for the full scope of the claims in view of the advanced state of the art and the level of disclosure provided:

*Wands* factor 1: The invention is directed to methods of inhibiting TACE without inhibiting MMP-1 by administering a hydroxamic acid compound.

*Wands* factor 2: Applicants submit that MMP-inhibitor research is an advanced area of research and there are numerous research programs directed to identifying MMP-inhibitors, as evidenced by the list of patents provided above.

*Wands* factor 3: Applicants respectfully submit that there is a reasonable prediction in the MMP-inhibitor art. The court in *Wands* remarked repeatedly that the standard was to be applied in a reasonable manner. If absolute predictability were the standard, it is unlikely that any invention would ever be found patentable.

*Wands* factor 4: In view of the extensive guidance as to the preparation and testing of hydroxamic acid compounds discussed above, Applicants submit that the specification as filed provides abundant support and instruction to teach those skilled in the art how to practice the invention. Applicants submit that the Examiner has not articulated any reason why one of skill in the art could not prepare the claimed compounds, identify the activity of compounds within the claims, formulate the claimed compounds into a pharmaceutical composition and administer it to a patient, based on the specification as filed.

*Wands* factor 5: The specification provides ample working examples of methods of preparing hydroxamic acid compounds such as those claimed, and methods of assaying the activity of those compounds in order to determine if they meet the claimed selectivity requirements.

*Wands* factors 6-7: The Examiner incorrectly concludes that those skilled in the art would not be able to use the invention based on the breadth of the claims and the content of the disclosure without undue experimentation. The Examiner has not presented any reasons why the implementation of the assays and the screening of the genus would present any difficulty to the skilled artisan. Applicants respectfully submit that there is no difficulty in reducing the invention to practice without undue experimentation, and therefore, the claims are enabled.

*Wands* factor 8: Applicants submit that based on an understanding of the pharmacology of MMP inhibitors, it should be acknowledged that the level of skill in the art is high.

Further, the facts of *Wands* also support the patentability of the instant claims. The Federal Circuit in *Wands* found that the PTO erred in rejecting the applicant's claim to immunoassay methods using a specified generic class of antibodies. The applicant made a public deposit of a hybridoma cell line that secreted only a specific antibody, but the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicant's written description, could produce and screen other hybridomas secreting other monoclonal antibodies falling within the generic class without undue experimenation. The situation in *Wands* is directly analogous to the case at hand. Applicants have claimed a method of selectively inhibiting an enzyme by administering a class of compounds. Applicants have disclosed a large representative number of compounds belonging to that class and a great deal is known in the art about other members of the class. Thus, all that the skilled artisan would need to do in order to reduce the instant invention to practice would be to produce and screen other hydroxamic acid compounds using the written description provided and the knowledge of the skilled artisan in this field. Thus, it is inappropriate to reject the instant invention because experimentation is required that amounts to nothing more than routine screening. The court in *Wands* clearly stated that mere screening does not amount to undue experimentation. However, the Examiner's entire argument is based on the conclusion that screening for compounds that meet the instant claims amounts to undue experimentation. In view of *Wands*, this conclusion is a faulty one.

The Examiner relies on the decision in *Genentech, Inc. v. Novo Nordisk*, 108 F.3d 1361 (Fed. Cir. 1997). He is invited to review this decision in more detail, as it clearly supports the patentability of Applicants' claims. Specifically, the question before the court was whether the specification would have enabled a person skilled in the art to use cleavable fusion expression to make human growth hormone (hGH) without undue experimentation. However, Genentech's disclosure did not describe in any detail how to make hGH using cleavable fusion expression, e.g., no reaction conditions for the steps needed to produce hGH were provided, nor was there a

description of any specific cleavable conjugate protein. The specification merely described three or four applications for which cleavable fusion expression was generally well-suited and then named an enzyme that might be used as a cleavage agent along with sites at which it cleaves. In arguing the patentability of the claims, Genentech focused exclusively on the level of skill in the art, arguing that any deficiency of the written description could be remedied by the skilled artisan without undue experimentation. But the court rejected this approach, holding that "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." *Id.* at 1366. The court concluded that

> Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. *Id.*

Contrary to the Examiner's opinion, *Genentech* is not analogous to the instant case. Applicants have provided assays for identifying compounds that may be used in the methods of the invention as well as compounds that meet the specified selectivity ranges. All that is needed of the skilled artisan to identify other compounds that meet the specified selectivity ranges is routine screening which the court in *Wands* held was not undue experimentation. In contrast, *Genentech* provided no disclosure in support of the claims and relied entirely on the skilled artisan to reduce the invention to practice. Nothing was provided within the four corners of the specification to enable the disclosure. However, Applicants have enabled compounds and methods identified by the claims, and the full scope of the claims can be realized by nothing more than routine experimentation, which is permissible.

The Examiner appears to have dismissed the *Wands* analysis in lieu of the decision in *Genentech* on the mistaken premise that *Genentech* has somehow rewritten the rule regarding undue experimentation. As discussed above, that is not the case and in fact, *Genentech* adds to rather than departs from the standard provided in *Wands*. Applicants respectfully submit that one must be careful not to misapply *Genentech*. Where no enabling disclosure is provided in a specification for a given claim and the applicant chooses to rely solely on what is known in the art to enable his invention, it is reasonable to say that he has not complied with the first paragraph of Section 112. However, where, as here, one provides an ample disclosure of the invention, including a method of making and using it, and all that the skilled artisan would need to do to expand on that disclosure amounts to nothing more than routine screening, neither *Genentech* nor *Wands* could be used as the basis for an enablement rejection.

In summary, an examination of the decisions in *Wands* and *Genentech* weighs heavily in favor of a finding that the present claims are fully enabled by the instant specification. Objectively, the specification teaches one skilled in the art how to make and use the invention. The Applicants have complied with the statutory requirements of § 112. The Examiner has not advanced any credible reason to establish that a person skilled in the art could not make and use the claimed

invention as a whole without undue experimentation. Applicants, therefore, request that the Examiner withdraw the rejection under 35 U.S.C. § 112, first paragraph.

## Conclusion

In light of the above arguments, legal precedents, and claim amendments, Applicants submit that the claims are in condition for allowance and such action is earnestly solicited. If after careful review of this Amendment, the Examiner maintains that there are issues that remain an impediment to allowance, he is invited to contact the undersigned in order to discuss such issues to expedite prosecution of this application.

Respectfully submitted,

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